REVIEWS

From MASK-air and SILAM to CATALYSE (Climate Action To Advance HeaLthY Societies in Europe)

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Abstract

Plant species vary under different climatic conditions and the distribution of pollen in the air. Trends in pollen distribution can be used to assess the impact of climate change on public health. In 2015, the Mobile Airways Sentinel networK for rhinitis and asthma (MASK-air®) was launched as a project of the European Innovation Partnership on Active and Healthy Ageing (EIP-on-AHA, DG Santé and DG CONNECT). This project aimed to develop a warning system to inform patients about the onset of the pollen season, namely, the System for Integrated modeLling of Atmospheric coMposition (SILAM). A global-to-meso–scale dispersion model was developed by the Finnish Meteorological Institute (FMI). It provides quantitative information on atmospheric pollution of anthropogenic and natural origins, particularly on allergenic pollens. Impact of Air Pollution on Asthma and Rhinitis (POLLAR, EIT Health) has combined MASK-air clinical data with SILAM forecasts. A new Horizon Europe grant (Climate Action to Advance HeaLthY Societies in Europe [CATALYSE]; grant agreement number 101057131), which came into force in September 2022, aims to improve our understanding of climate change and help us find ways to counteract it. One objective of this project is to develop early warning systems and predictive models to improve the effectiveness of strategies for adapting to climate change. One of the warning systems is focused on allergic rhinitis (CATALYSE Task 3.2), with a collaboration between the FMI (Finland), Porto University (Portugal), MASK-air SAS (France), ISGlobal (Spain), Hertie School (Germany), and the University of Zurich (Switzerland). It is to be implemented with the support of the European Academy of Allergy and Clinical Immunology. This paper reports the planning of CATALYSE Task 3.2.

Key words: CATALYSE. MASK-air. SILAM. Pollen. Climate change.

Resumen

Las especies de plantas varían según las diferentes condiciones climáticas y la distribución del polen en el aire, y sus tendencias pueden utilizarse para evaluar el impacto del cambio climático en la salud pública. En 2015, se lanza MASK-air® (Mobile Airways Sentinel network for rhinitis and asma) como un proyecto de la Asociación Europea de Innovación sobre Envejecimiento Activo y Saludable (EIP-on-AHA, DG Santé y DG CONNECT), que tenía como objetivo desarrollar un sistema de alerta para informar a los pacientes sobre el inicio de la temporada de polen. Paralelamente, SILAM (Sistema para el modelado integrado de la composición atmosférica), un modelo de dispersión de escala global a meso, ha sido desarrollado por el Instituto Meteorológico de Finlandia (FMI) y proporciona información cuantitativa sobre la contaminación atmosférica de origen antropogénico y natural, en particular sobre los pólenes alergénicos. El proyecto POLLAR (Impacto de la contaminación del aire en el asma y la rinitis, EIT Health) combina los datos clínicos de MASK-air® con las previsiones de SILAM. Una nueva subvención de Horizon Europe, CATALYZE (Climate Action to Advance HeaLthY Societies in Europe; acuerdo de subvención número 101057131), que comenzó en septiembre de 2022, tiene como objetivo comprender mejor el cambio climático y encontrar formas de contrarrestarlo. Uno de los objetivos de este proyecto es desarrollar sistemas de alerta temprana y modelos predictivos para mejorar la eficacia de las estrategias de adaptación al cambio climático. Uno de los sistemas de alerta se centra en la rinitis alérgica (CATALYSE Task 3.2) siendo desarrollado mediante una colaboración entre la FMI (Finlandia), la Universidad de Oporto (Portugal), MASK-air® SAS (Francia), ISGlobal (España), Hertie School (Alemania) y la Universidad de Zúrich (Suiza), y se implementará con el apoyo de la EAACI. Este documento se centra en la planificación de CATALYZE Task 3.2.

Palabras clave: CATALYSE. MASK-air®. SILAM. Polen. Cambio climático.

Introduction and Concept

Allergic diseases (eg, allergic rhinitis [AR], asthma, rhinoconjunctivitis, urticaria, and eczema) are among the most common diseases in the world [1]. They generate a substantial burden for social life, work, and school performance [2-5]. Many patients remain untreated, and symptoms are often uncontrolled [6,7].

Climate change is associated with an increased prevalence and severity of rhinitis and asthma [8,9]. Plant species vary under different climatic conditions, and the distribution of pollen can be used to assess the impact of climate change. Worsening ambient air pollution and changes in temperature, humidity, and wind for atmospheric transport (leading to altered local and regional allergen production [10]), as well as reduced biodiversity, play a decisive role in the worsening of rhinitis and asthma symptoms, with potentially relevant implications for clinical practice and public health planning [11]. "The 2022 Europe report of the Lancet Countdown on health and climate change: towards a climate-resilient future" has proposed allergenic trees as an indicator of climate change [12].

mHealth apps can help to better understand and mitigate climate change. One such example is the Mobile Airways Sentinel networK for rhinitis and asthma (MASK-air®), which was launched in 2015 as a project of the European Innovation Partnership on Active and Healthy Ageing (EIP-on-AHA, DG Santé and DG CONNECT). At that time, it envisioned not only the possibility of patients reporting their daily allergy symptoms and medication through an mHealth app, but also the development of an SMS-based early warning system informing patients about the beginning and the peak of the pollen season (Figure 1). This is reflected in the following statement: "For patients allergic to pollen, knowledge of the onset of the pollen season is of vital importance in order to start treatment as early as possible for the control of symptoms. When travelling, patients are often concerned about potential symptoms and/or bothered by symptoms outside their usual symptom 'window'. It is therefore of importance to forecast the onset of the pollen season and to characterize seasons in different places" [7].

While this SMS-based early warning system has not yet been developed, some advances have been made toward the prediction of allergy risk for sensitive individuals at the European level. The System for Integrated modeLling of Atmospheric coMposition (SILAM) provides air quality forecasts on a global scale, although pollen predictions are currently limited in Europe owing to the absence of representative habitation maps (with good resolution) of allergenic plants and pollen observations in other regions. The expansion of SILAM pollen forecasts to other continents is planned. In particular, a combination of operational forecasts of air quality and pollen concentrations of the SILAM dispersion model (http://silam.fmi.fi) was used to reproduce the complex interaction between exacerbating factors of environmental allergy (Figure 2). Since air pollutants are known to worsen pollen-related allergy, the allergy risk index formula includes the pollen levels amplified locally by poor air quality [13].

A new Horizon Europe grant, Climate Action to Advance HeaLthY Societies in Europe (CATALYSE; grant agreement number 101057131) came into force in September 2022. Its

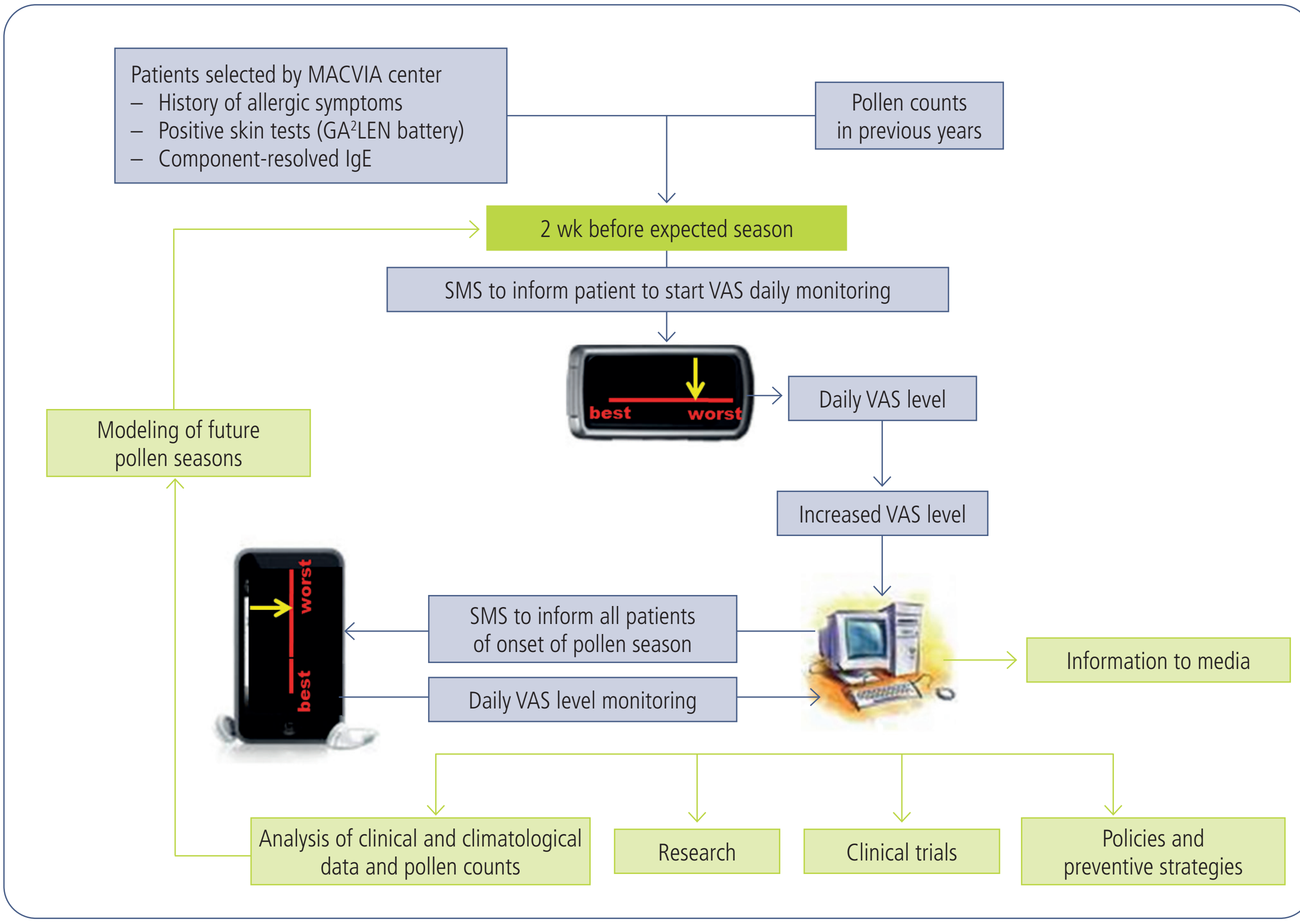

Figure 1. The MASK-air® sentinel network proposed in 2015 (from [7]). MACVIA-LR: European Innovation Partnership on Active and Healthy Ageing. VAS, indicates visual analog scale.

aim is to better understand climate change and to find ways to counteract it. One of the specific objectives of this project is to develop early warning systems and predictive models to improve the effectiveness of strategies for adaptation to climate change. One of the early warning systems to be developed is focused on AR (CATALYSE Task 3.2). It stems from a collaboration between the Finnish Meteorological Institute (FMI), Porto University, MASK-air SAS, ISGlobal, the Hertie School, and the University of Zurich. The development of this early warning system will encompass the following: (*i*) the integration of information technology tools for climate, weather, air pollution, and aerobiology in MASK-air®, along with patients' previously-reported symptoms; and (*ii*) social media data (Google Trends and Twitter data) [14]. The European Academy of Allergy and Clinical Immunology will support its implementation and assist further development with the expertise of the major European allergy societies. Citizens will thus be informed of personal environmental threats, which may also be linked to indicators of planetary health and sustainability.

Therefore, a direct link and cross-fertilization can be established between the aims and the achievements of MASK-air®, SILAM, and CATALYSE. The functionality of MASK-air®, enriched with developments in SILAM in the Impact of Air Pollution on Asthma and Rhinitis project (POLLAR, EIT Health) [12], will form the background to building an early warning system for AR within CATALYSE. For its part, CATALYSE will provide extremely important tools in order to bring the MASK-air® predictions to a new technological level, specifically through the development of an alert system that utilizes internet search activity and severity of reported allergy/rhinitis symptoms of individual app users across Europe.

Existing CATALYSE Allergy-Related Technologies

MASK-air® (Annex I)

MASK, the Phase 3 Allergic Rhinitis and its Impact on Asthma (ARIA) initiative [3,15], is a flexible e-platform for AR and asthma and includes the MASK-air® app. It is operational in 27 countries and 19 languages. Over 58 000 users have been registered.

MASK-air® is a validated mHealth app (Medical Device regulation Class IIa) and a Good Practice of DG Santé in digitally enabled, patient-centered care (Annex 1) [16]. It is

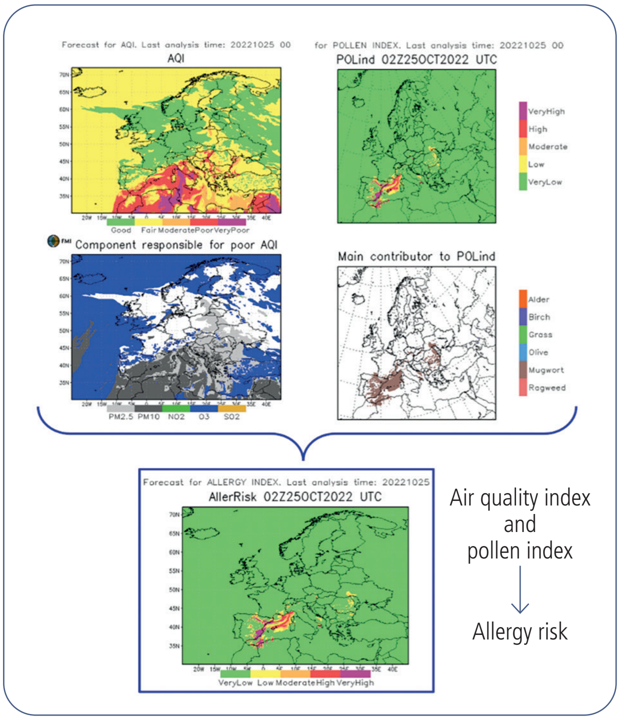

Figure 2. Allergy risk prediction by the SILAM model: single forecast example for 25 Oct 2022. SILAM indicates System for Integrated modeLling of Atmospheric coMposition

also a candidate for Good Practice of the Organisation for Economic Co-operation and Development. The maturity level of MASK-air® tools assessed by technology readiness level [17] ranges from 7 to 9/9 [18]. The vision of MASK-air® has led to a strategic overview that was initiated by ARIA in 1999. It includes WHO-associated projects [3,19], as well as EU grants and projects [20-26].

MASK-air® data have enabled the discovery and characterization of novel phenotypes, as well as novel insights into the management of AR. MASK-air® data have shown that most AR patients are not adherent and do not follow guidelines, use as-needed treatment, do not take medication when they are well, increase their treatment based on symptoms, do not use the recommended treatment, and do not always report better control (symptoms, work productivity, educational performance) when using medications. A combined symptom-medication score (ARIA, EAACI, and combined symptom and medication score [CSMS]) has been developed and validated for clinical practice and trials. The implications of the novel MASK-air® information should lead to changes in the management of rhinitis and asthma [27].

Embedding SILAM Predictions in MASK-air®: POLLAR

AR is impacted by allergens and air pollution, although interactions between air pollution, sleep, and allergic diseases have been insufficiently understood. POLLAR, a project of the European Institute of Innovation and Technology (EIT Health) and a demonstration project of the Global Alliance against Chronic Respiratory Diseases, WHO) [28,29] used MASK-air® to investigate these relationships in Northern and Central European users in 2017 and 2018 [26]. A total of 3323 geolocated individuals (36 440 days on which the MASK-air® daily monitoring questionnaire had been completed) were studied. Associations between uncontrolled rhinitis and pollutants were stronger during the grass pollen season [30], and an interaction was detected between ozone and grass pollen but not birch pollen. A similar trend was found for particulate matter with a diameter of less than 2.5 µm, especially in 2017. These results suggest that the relationship between uncontrolled AR and air pollution is modified by the presence of grass pollens and favor the inclusion of pollen and pollution data in MASK-air®.

Following the POLLAR study, and within that framework, a new index developed by the FMI has been made available in MASK-air® [13]. For geolocated users, MASK-air® provides a daily prediction of pollen levels indicated for the current day and for the following day. Geolocation-based forecasts of pollution levels are available within MASK-air®. In CATALYSE, the predictive model for the user symptoms will be built depending on personal sensitivity to the complex of environmental factors (air quality + pollen). It will be based on an updated symptom prediction model specifically including individual changes in user symptoms as a reaction to changes ("increment") in environmental conditions.

SILAM® Pollen Predictions (Annex II)

Pollen forecasting models for alder, birch, grass, mugwort, olive, and ragweed are integral parts of SILAM (http://silam.fmi.fi/, open-source code https://github.com/fmidev/silam-model/ visited 25.10.2022) [31]. This advanced atmospheric composition model is in operational use in Finland. It also routinely provides air quality and pollen forecasts to the Copernicus Atmospheric Monitoring Service (https://atmosphere.copernicus.eu/) and to various research and application projects. The pollen lifecycle in the atmosphere within SILAM (such as release, transport, mixing, and removal) is formulated in the same way as for a chemically nonreactive aerosol, taking into account the density and aerodynamic diameter of pollen grains. To reproduce the natural biological cycles of pollen presentation, maturation, and release by plants, 2 types of phenological models were developed in SILAM. The parametrization of tree phenology (for alder, birch, and olive) is based on the concept of accumulated heat as the main trigger and driver of the flowering season [32-34]. The pollen season characteristics for herbaceous plants were empirically derived from long-term aerobiological pollen measurements and used in the model as a fixed pollen calendar. The habitat maps for each taxon delineate the geographical areas where SILAM first reports on the pollen release from allergenic plants. The propagation of the pollen season is modulated by the actual meteorological conditions.

The quality of SILAM air quality predictions is regularly evaluated by direct comparison of model forecasts with the air quality and pollen measurements within the scope of several international projects and operational services, such as the Copernicus Atmospheric Monitoring Service, https://atmosphere.copernicus.eu/, visited 22.11.2022), the International Cooperative for Aerosol Prediction [35] (https://doi.org/10.1002/qj.3497), the World Meteorological

Organization Global Air Quality Forecasting and Information System (https://hpfx.collab.science.gc.ca/~svfs000/na-aq-mm-fe/dist/, visited 22.11.2022), the World Meteorological Organization Sand and Dust Storm Warning Advisory and Assessment System (https://dust.aemet.es, visited 24.11.2022), and other national and international evaluation projects.

CATALYSE

Pollen in Climate Change

Exposure to sensitizing pollens, one of the main triggers of AR symptoms, is predicted to increase owing to climate change–induced increases in the duration of allergenic pollen seasons, pollen concentrations, and allergenicity [36-39]. This is not unexpected, since the timing of the life cycle events for plants is generally sensitive to temperature, with atmospheric pollen levels and pollen spread also being influenced by humidity and carbon dioxide levels [37]. In particular, higher temperatures and increased carbon dioxide levels have been found to be associated with higher pollen production in experimental greenhouse and growth chamber studies, with some longer-term observational studies having found correlations between temperature and pollen concentrations or pollen season length [36,40].

CATALYSE Task 3.2 – Early Warning System for Allergic Rhinitis

The primary objective of CATALYSE task 3.2 is to develop an early warning system for AR, rhinoconjunctivitis, and asthma. This system is set to incorporate data on meteorological forecasting, air quality (including air pollution), allergenic pollen levels, previously reported symptoms, and Internet users' activity. These data will then allow for the generation of early warnings on the possibility of short-term exacerbations due to environmental conditions.

More specifically, the SILAM model will provide hourly forecasts of air quality, meteorological parameters (eg, temperature and humidity), and pollen concentrations over Europe with a horizontal resolution of about 10 km × 10 km for 6 relevant allergic pollen species in Europe: alder, birch, grass, mugwort, olive, and ragweed. These data will form the basis for constructing the space-resolving models, indicating the overall risk of short-term respiratory allergy exacerbations for each European region. The SILAM pollen/allergy risk forecasts will be generated on the regular Mercator projection (longitude-latitude grid with horizontal resolution about 10 km × 10 km). Using these gridded forecasts, the predictions can be interpolated into or added to any Nomenclature of Territorial Units levels. Such models will be interconnected with MASK-air® and further personalized by including patients' previously reported symptoms in MASK-air®. For patients who had previously reported a small amount of data to MASK-air®, we may—in order to personalize the model—use data from other users reporting MASK-air® data in the same region and Twitter posts and Internet search activity data on AR (assessed by Google Trends, https://trends.google.es/trends/). The latter will be particularly useful for regions where MASK-air®-reported data are sparse and will be based on previous studies indicating that Google Trends searches correlate well with surveillance data on rhinitis and asthma or with asthma hospitalizations [14,41]. The Bayesian multilevel estimation with poststratification approaches will be used to address limitations in the representativeness of social media data, particularly at the higher level of geographical granularity relevant for MASK-air® users.

The predictive skill of the early warning system will be tested initially on the retrospective data sets of MASK-air®, with assessment and prediction aimed at patients and regions reporting larger and smaller volumes of data. This system will be further validated in terms of real-world utility through 3 case studies in different regions of Europe (Southern, Central, and Northern). The validation will involve a randomized trial to assess the utility of personalized messages delivered through the MASK-air® early warning system to improve symptom management. In brief, enrolled patients will be using MASK-air® and will be randomized to receive personalized messages based on early warning systems or "neutral" general messages that may help them to adopt protective measures. The primary outcome will consist of the recently developed and validated EAACI-ARIA allergy CSMS [42]. Secondary outcomes will include reported visual analog scale scores for allergy symptoms and medication use.

Supporting Studies

The development of the early warning system will require supporting studies to be conducted, gaps in current knowledge to be filled, and, possibly, the development of the early warning system to be optimized. Such supporting studies include the following:

- Assessment of the MASK-air® reporting patterns according to the social and economic development of the region: Using data from geolocated European users, we may understand whether the region in which the patient lives influences the patterns of using MASK-air®, as well as the reporting of symptoms and medication. This approach may inform on the representativeness of MASK-air® reported days, health policies to reduce inequalities within and between countries, and differences by sex.
- The study of the characteristics of reported vs unreported days in MASK-air®: In order to assess the potential selection biases associated with the days on which patients report MASK-air® data, we shall assess whether reported and unreported days differ substantially depending on environmental exposure variables (eg, pollen and pollution). Pollens can induce nasal and/or ocular symptoms within a few minutes, as shown by allergen challenge [42]. This study may also enable imputation using models accounting for unreported days in MASK-air®, thus further facilitating the implementation of longitudinal studies, better assessment of climate change, and clinical trials.
- Assessment of the birch or grass pollen levels in European MASK-air® users associated with different levels of AR and asthma using defined cut-offs for well-controlled, partly controlled, and poorly controlled symptoms [43]: This study should result in the identification of pollen level thresholds that will implement personalized

and regionalized warnings of pollen levels that could potentially induce symptoms or severe symptoms. Such assessment will prove very important in clinical trials.

Potential Limitations

Implementation of MASK-air® is subject to limitations. In particular, MASK-air® is only available in 22 European countries, limiting the coverage of the personalized early warning system to those countries. However, the countries in which MASK-air® is available comprise 90% of the population of the European Union. Another limitation may stem from the relatively low number of users reporting a high frequency of MASK-air® data, thus limiting the total number of users receiving fully personalized information on their allergy risk.

SILAM pollen forecasts—currently available for 12 pollen species—appear to be more accurate in Northern and Central Europe than in Southern Europe, where human-controlled local watering significantly affects plant phenology [43,44]. The connection of the gridded atmospheric information (resolution 10 km × 10 km) with individual-level health data (MASK-air®) must be tested and recorded for every grid cell separately. Multiuser contribution per grid cell will be averaged and combined with the "neutral"/"background" allergy risk value (which is computed based on health data and pollen indices).

Conclusion

In 2015, when MASK-air® was launched, the development of a personalized early warning system (warning patients about the possibility of rhinitis exacerbations) had been envisioned [7]. While some steps were taken to achieve this goal (with the incorporation, in MASK-air®, of geolocalized forecasts for pollen levels), such a warning system is still lacking. CATALYSE presents an opportunity for the development and validation of a personalized early warning system incorporating environmental data, symptoms, and online activity data. The inclusion of a task on allergic respiratory diseases in CATALYSE reflects not only the burden of this disease, but also the expected increase in its prevalence and severity as a result of climate change.

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Conflicts of Interest

JB reports personal fees from Cipla, Menarini, Mylan, Novartis, Purina, Sanofi-Aventis, Teva, Uriach, KYomed-Innov, and Mask-air-SAS, outside the submitted work.

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MO reports personal fees from Hycor Diagnostics outside the submitted work and is the Scientific Co-Founder of Tolerogenics SARL, Luxembourg.

TH reports personal fees from Orion Pharma, outside the submitted work.

HH reports personal fees from Orion Pharma, outside the submitted work.

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The remaining authors declare that they have no conflicts of interest.

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